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A. Piette, G. Verschraegen

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1 **Role of coagulase-negative staphylococci in human disease.**

2 A. Piette\*, G. Verschraegen

3 Department of Microbiology, University Hospital Ghent, Belgium

4 De Pintelaan 185, 9000 Gent

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6 \* Corresponding author. Tel.: +32 9 3326639; Fax: +32 9 3324985

7 E-mail address: [anne.piette@ugent.be](mailto:anne.piette@ugent.be)

8

9

Accepted Manuscript

9 **Abstract**

10

11 Coagulase-negative staphylococci (CNS) are normal inhabitants of human skin and mucous  
12 membranes. They have long been dismissed as culture contaminants, but now the potentially  
13 important role of CNS as pathogens and their increasing incidence has been recognized.  
14 Approximately 55%-75% of nosocomial isolates is methicillin resistant. CNS were the first  
15 organisms in which glycopeptide resistance was recognized. In the immunocompetent host, CNS  
16 endocarditis and urinary tract infections with *Staphylococcus saprophyticus* are the most common  
17 CNS infections. Other patients are usually immunocompromised, with indwelling or implanted  
18 foreign bodies. CNS account for approximately 30% of all nosocomial blood stream infections. The  
19 majority of these concern catheter-related sepsis. Other important infections due to CNS include  
20 central nervous system shunt infections, endophthalmitis, surgical site infections, peritonitis in  
21 patients with continuous ambulatory peritoneal dialysis and foreign body infections. CNS are rarely  
22 associated with mastitis in humans. *Staphylococcus lugdunensis* is more pathogenic than other CNS  
23 as it expresses several potential virulence factors. The distinction between clinically significant,  
24 pathogenic and contaminating isolates is a major problem. Several studies show clonal intra and inter  
25 hospital spread of *Staphylococcus epidermidis* strains which suggests that infection control measures  
26 may be necessary for multiresistant CNS isolates as for methicillin resistant *Staphylococcus aureus*.  
27 As a result of medical progress, mainly due to the use of invasive and indwelling medical devices,  
28 CNS are now a major cause of nosocomial and health-care related infections.

29 **Keywords:** coagulase-negative staphylococci, human medicine, species distribution, antibiotic  
30 resistance, endocarditis, urinary tract infections, blood stream infections, nosocomial infection

31

## 31 1. Introduction

32

33 Coagulase-negative staphylococci (CNS) are normal inhabitants of human skin and mucous  
34 membranes. They were first described in 1884 by Rodenbach as *Staphylococcus albus*, an avirulent  
35 staphylococcus. They have long been dismissed as culture contaminants, even in type 1 samples  
36 (samples obtained from a normally sterile site by needle aspiration or surgery). Only in 1958 the first  
37 report on the potential pathogenicity of CNS in patients with septicaemia was published (Smith et al.,  
38 1958). Later on, casuistic reports of CNS endocarditis, wound and urinary tract infections (UTI)  
39 appeared (Kloos et al., 1994). Since the 1970s, CNS are recognised as etiologic agents of a wide  
40 variety of infections. Patients with CNS infections are usually immunocompromised, with indwelling  
41 or implanted foreign bodies. CNS play a role in bacteraemia, central nervous system shunt infection,  
42 endocarditis, urinary tract infection, surgical site infections, endophthalmitis, foreign body infection  
43 and many other infections. The distinction between clinically significant, pathogenic and  
44 contaminating isolates is difficult and remains a major problem.

45 An overview of the medical literature on CNS is given, with special focus on identification,  
46 species distribution, virulence factors, antibiotic resistance, epidemiology and specific infections  
47 caused by CNS in humans.

48

## 49 2. Identification

50

51 Before 1975, *S. albus* or *S. epidermidis* was distinguished from *S. aureus* by the inability to  
52 clot blood plasma. Today, tests based on coagulase production and the thermonuclease reaction are  
53 used for rapid differentiation of *S. aureus* from other staphylococcal species (Huebner et al., 1999).  
54 Currently, 39 species of CNS are recognized (Euzéby, 2007). Sixteen of these species have been  
55 found in specimens of human origin. They are grouped in novobiocin-resistant species (*S. cohnii*, *S.*  
56 *saprophyticus*, *S. sciuri*, *S. xylois*) and novobiocin-susceptible species (*S. auricularis*, *S. capitis*, *S.*

57 *caprae*, *S. epidermidis*, *S. haemolyticus*, *S. hominis*, *S. lugdunensis*, *S. pasteurii*, *S. saccharolyticus*, *S.*  
58 *schleiferi*, *S. simulans*, *S. warneri*) (von Eiff et al., 2001).

59 Accurate identification of CNS isolates to species level is difficult to perform and expensive.  
60 According to Huebner et al., 1999, identification to species level is, in general, not necessary for  
61 good patient management. However, recent literature indicates accurate species identification is  
62 necessary to provide a better understanding of pathogenic potential of various CNS species (Heikens  
63 et al., 2005; Sivadon et al., 2005).

64 Before 1975, CNS were classified in different biotypes, according to Baird-Parker. In 1975,  
65 Kloos and Schleifer proposed a scheme for identification of staphylococci in the routine laboratory.  
66 This scheme is based on 13 key characteristics, such as coagulase activity, hemolysis, nitrate  
67 reduction and aerobic acid production from carbohydrates (Kloos et al., 1975). Nowadays, besides  
68 phenotypic methods, a variety of genotypic methods (16S rRNA, *sodA*, *gap*, *rpoB*, *tuf* gene  
69 sequencing) have been developed (Heikens et al., 2005; Layer et al., 2006; Mellmann et al., 2006).  
70 Heikens et al. compared phenotypic with genotypic (16S rRNA gene and *tuf* gene sequencing)  
71 identification (Heikens et al., 2005). The results showed that *tuf* gene sequencing is the best  
72 identification method (5 of 57 isolates misidentified). The API staph ID test (BioMérieux, Marcy  
73 l'Etoile, France) appeared to be a reliable alternative (7 of 57 isolates misidentified). The  
74 performance of the BD Phoenix system (Becton Dickinson Diagnostic Systems, Sparks, MD, USA)  
75 was poor. A recent study (Layer et al., 2006) compared 3 phenotypic, commercial identification  
76 methods with a molecular identification method (*gap* based terminal restriction fragment length  
77 polymorphism analysis) as reference method. The BD Phoenix ID-13 system (Becton Dickinson  
78 Diagnostic Systems) identified 18 of 27 reference strains and 70 of 86 clinical isolates correctly, the  
79 VITEK 2 ID-GP system (BioMérieux) 20 of 27 reference strains and 80 of 86 clinical isolates, the ID  
80 32 STAPH system (BioMérieux) 23 of 27 reference strains and 19 of 20 clinical isolates. Thus,  
81 genotypic methods are superior to phenotypic methods, but some phenotypic methods have a highly

82 acceptable level of identification accuracy when used in routine practice (Heikens et al., 2005; Layer  
83 et al., 2006).

84

### 85 **3. Species distribution**

86

87 Interpretation and comparison of the species distribution found in different studies is very  
88 difficult. The type of identification method used, may influence the species distribution found and  
89 some *Staphylococcus* species demonstrate habitat or niche preference. *S. capitis* for example is  
90 mainly found on the adult head, *S. cohnii* on the feet. *S. saprophyticus* is found in urine of young  
91 women (Kloos et al., 1994; Bannerman, 2003).

92 *S. epidermidis*, *S. haemolyticus* and *S. hominis* are the most frequently encountered CNS  
93 species in clinical samples. The isolation frequency of the different CNS species in clinical, human  
94 specimens is shown in Table 1. Usually, more than 50% of CNS isolates belong to the species *S.*  
95 *epidermidis*. In India, low percentages of *S. epidermidis* were found (13.2%) and high percentages of  
96 *S. haemolyticus* (71.9%) (Chaudhury et al., 2007). A Japanese study (Kawamura et al., 1998) found a  
97 very high percentage of *S. caprae* (14%), while the frequency of isolation in other studies is very  
98 low. In the study by Kawamura et al., 1998, all isolates were identified by a DNA-DNA  
99 hybridisation and by conventional, phenotypic identification based on the Kloos and Schleifer  
100 method. None of the *S. caprae* isolates was identified correctly by the phenotypic method.

101 In Spanish point prevalence studies in a large group of hospitals, performed from 1986 to  
102 2002, showed no major shifts in the distribution of CNS species (Cuevas et al., 2004). When the  
103 distribution in 2002 is compared with 1986, there is a decrease in isolation of *S. epidermidis*, *S.*  
104 *simulans*, *S. cohnii* and *S. xylois* and an increase in isolation of *S. hominis* and *S. saprophyticus*.

105 *S. epidermidis* is the predominant pathogen in intravascular catheter-related infections, nosocomial  
106 bacteremia, endocarditis, urinary tract and surgical wounds infections, central nervous system shunt  
107 infections, ophthalmologic infections, peritoneal dialysis-related infections and infections of

108 prosthetic joints (Bannerman, 2003). *S. haemolyticus* has been implicated in native valve  
109 endocarditis, septicemia, urinary tract infections, peritonitis and wound, bone and joint infections  
110 (Bannerman, 2003). *S. saprophyticus* is associated with urinary tract infections in young females. *S.*  
111 *lugdunensis* has been implicated in arthritis, catheter infections, bacteremia, urinary tract infections,  
112 prosthetic joint infections and endocarditis (Bannerman, 2003). Other CNS species have been  
113 implicated in a variety of infections.

114

#### 115 **4. Virulence factors**

116

117         Already in 1972, the “slime” production of CNS was noted as an important factor in the  
118 pathogenesis of infections (Huebner et al., 1999). This “slime” or biofilm is the most important  
119 virulence factor of *S. epidermidis*. The biofilm formation enables attachment and persistence of the  
120 bacteria on foreign materials. Moreover, bacteria organized in biofilms are protected from the action  
121 of antibiotics and the immune system (Costerton et al., 1999; Mack et al., 2007). The first phase in  
122 biofilm formation is attachment, in which staphylococcal binding proteins such as the  
123 autolysin/adhesins AtlE and Aae, the fibrinogen-binding protein Fbe/Sdrg, the fibronectin-binding  
124 protein Embp and the lipase GehD, play an important role (Mack et al., 2007). The most important  
125 adhesion molecule is AtlE. The second phase in biofilm formation is accumulation, in which the  
126 polysaccharide intercellular protein PIA, encoded by the *icaADBC* locus, is a major functional  
127 component (von Eiff et al., 2002; Mack et al., 2007). In strains lacking the *icaADBC* locus, biofilm  
128 formation is mediated by the accumulation-associated protein (Aap) or by the biofilm-associated  
129 protein (Bap/Bhp) (Ziebuhr et al., 2006). Recently, 2 biofilm producing strains, negative for PIA,  
130 Aap and Bhp, have been described (Qin et al., 2007). The regulation of biofilm formation is very  
131 complicated and best studied in *S. epidermidis*. Different regulatory systems, such as *sae*, alternative  
132 sigma factor  $\sigma^B$ , *sar* and quorum sensing (this is inter and intra species communication, possible  
133 when a certain bacterial density has been established) systems play a role (Xu et al., 2006; Mack et

134 al., 2007). The 2 quorum sensing systems in *S. epidermidis*, *agr* and *luxS/AI-2*, repress the biofilm  
135 formation: *luxS* system by downregulating PIA production, *agr* system by downregulating AtlE  
136 production. *Agr* controls the expression of toxins and secreted virulence factors and the interaction  
137 with the immune system (Kong et al., 2006). Quorum sensing systems have potential as therapeutic  
138 targets for control of staphylococcal infections (Harraghy et al., 2007). Another important virulence  
139 factor of CNS is the antibiotic resistance. Regulation of biofilm formation and methicillin resistance  
140 seem to use similar pathways, as insertion of a certain transposon influences both biofilm formation  
141 and the expression of methicillin resistance (Mack et al., 2007). Methicillin resistance was found to  
142 be significantly higher in slime positive isolates (81%) than in slime negative isolates (57%) (Koksal  
143 et al., 2007).

144 The phenotypic variability and heterogeneous gene expression observed in CNS, especially in  
145 *S. epidermidis*, is an advantage for adaptation to changing environmental conditions (Ziebuhr et al.,  
146 2006).

147 Other potential virulence factors of *S. epidermidis* include the following: extracellular  
148 enzymes and toxins: metalloprotease with elastase activity, cysteine protease, serine protease, lipase,  
149 fatty acid modifying enzymes (FAME) and the  $\delta$ -toxin. CNS also produce lantibiotics (von Eiff et  
150 al., 2002; Vuong et al., 2002). Lantibiotics are bacteriocins such as epidermin, which are active  
151 against other gram-positive bacteria.

152 Several studies tried to discriminate between invasive and commensal *S. epidermidis* strains  
153 by the detection of virulence associated genes (Frebourg et al., 2000; Vandecasteele et al., 2003;  
154 Rohde et al., 2004). In the study by Rohde et al (Rohde et al., 2004) the virulence genes *icaADBC*,  
155 *mecA* and IS256 were all highly prevalent in invasive strains. Commensal strains from healthy  
156 individuals almost completely lacked *icaADBC*, *mecA* and IS256. However in the commensal  
157 strains isolated from hospitalized bone marrow transplant patients the studied genes had the same  
158 distribution as the invasive strains, suggesting replacement of their own commensal flora by hospital  
159 strains. As a consequence these genes cannot discriminate between invasive and commensal strains.

160 *S. lugdunensis* and *S. schleiferi* are more pathogenic than other CNS species. Like *S. aureus*,  
161 they may express a clumping factor and/or produce a thermostable DNase (von Eiff et al., 2002). A  
162 variable percentage of these strains produces extracellular slime or glyocalix, esterase, FAME,  
163 protease, lipase and a haemolysin. *S. lugdunensis* is more likely than other CNS, to be considered a  
164 pathogen until proven otherwise (Poutanen et al., 2001; Koziol-Montewka et al., 2006). *S.*  
165 *lugdunensis* is often misidentified as *S. aureus*, because slide agglutination tests are often positive.

166 The main virulence factor of *S. saprophyticus* in UTI is the capacity to adhere to uroepithelial  
167 cells by means of surface-associated proteins: the autolysin/adhesin Aas, Ssp and Sdrl. Once  
168 colonization has been established several invasion factors are produced: urease, elastase, lipase and  
169 FAME (von Eiff et al., 2002).

170

## 171 **5. Antibiotic resistance**

172

173 Resistance to antibiotics in CNS is of major concern. Penicillin resistance in CNS is very  
174 high: even in 1968 the resistance rate was 60% (Corse et al., 1968). Nowadays, resistance is around  
175 91% in clinical strains (Cuevas et al., 2004; Koksall et al., 2007). Methicillin resistance in  
176 staphylococci is caused by expression of PBP2a encoded by the *mecA* gene. *MecA* is located on a  
177 genetic element called the staphylococcal cassette chromosome (SCC). There is evidence of  
178 horizontal transfer of SCC cassettes between staphylococcal species (Hanssen et al., 2004), which  
179 implies that CNS could serve as a reservoir for the spread of resistance genes to *S. aureus*. In clinical  
180 samples, rates of methicillin resistance of 55% - 77% and even 86% in ICU settings, have been  
181 reported (Del' Alamo et al., 1999; Agvald-Öhman et al., 2004; Cuevas et al., 2004; Chaudhury et al.,  
182 2007; Gatermann et al., 2007; Jones et al., 2007a; Jones et al., 2007b; Koksall et al., 2007; Sader et  
183 al., 2007;). In continuous ambulatory peritoneal dialysis (CAPD) patients and medical students 38%  
184 and 27%, respectively, of colonizing CNS strains were methicillin resistant (de Mattos et al., 2003;  
185 Koziol-Montewka et al., 2006; Higuchi et al., 2007). Several studies show an increase of MR CNS

186 over time. In Spain, methicillin or oxacillin resistance remained stable (26%-34% of CNS) between  
187 1986 and 1994, increased significantly in 1996 (51%) and reached 61% in 2002 (Cuevas et al.,  
188 2004). An increase of methicillin resistant CNS strains was also found in other studies: from 38% in  
189 1996 to 68% in 2007 in blood of patients with true bacteremia (Koksal et al., 2007), from 19% in  
190 1991 to 74% in 1998 in peritoneal dialysis patients (Zelenitsky et al., 2000). It is generally assumed  
191 that approximately 80% of nosocomial isolates and 30-40% of isolates obtained from healthy carriers  
192 or patients from the community, demonstrate resistance to methicillin (Huebner et al., 1999; de  
193 Mattos et al., 2003; Koziol-Montewka et al., 2006).

194 In Spain, resistance to ciprofloxacin and erythromycin increased progressively in CNS from  
195 1% and 41% in 1986 to 45% and 63% in 2002 (Cuevas et al., 2004). Susceptibility percentages to  
196 different antibiotics are given in Table 2. Two surveillance studies, performed in 2006, one in the US  
197 and one in Europe, Asia, Australia and Latin America show comparable susceptibility results.  
198 Susceptibility rates to fluoroquinolones, erythromycin, clindamycin, trimethoprim/sulfamethoxazole,  
199 gentamicin, teicoplanin and linezolid are 42%-47%, 30%-34%, 60%-61%, 62%-59%, 71%-58%, 99  
200 and 98-99%, respectively (Jones et al., 2007a, Jones et al., 2007b). Methicillin resistant strains have  
201 high rates of resistance to other classes of antibiotics. Resistance rates in methicillin susceptible  
202 strains are much lower (Reynolds et al., 2004; Biedenbach et al., 2007; Koksal et al., 2007; Sader et  
203 al., 2007).

204 CNS were the first organisms in which acquired glycopeptide resistance (vancomycin MIC  
205  $\geq 8$   $\mu\text{g/mL}$ , teicoplanin MIC  $\geq 16$   $\mu\text{g/mL}$ ) was recognized (Biavasco et al., 2000). Most of the clinical  
206 glycopeptides resistant isolates are resistant to teicoplanin, but susceptible to vancomycin, indicating  
207 a heterogeneous expression of glycopeptides resistance (Nunes et al., 2006). The resistance  
208 mechanisms to glycopeptides in CNS are not yet fully understood. Most reports show that resistance  
209 mechanism in CNS is similar to that described in VISA and hetero-VISA strains (Nunes et al., 2006).  
210 This mechanism is multifactorial, expression related and can be selected, in vitro, by exposure to  
211 teicoplanin and vancomycin (Biavasco et al., 2000; Nunes et al., 2006). Laboratory detection of

212 glycopeptide-resistance may be problematic, as there is an influence of various technical factors.  
213 Susceptibility testing by disk diffusion results in a very high percentage of false susceptible results  
214 (very major errors in 80% of the nonsusceptible to teicoplanin strains) (Del' Alamo et al., 1999).  
215 Susceptibility rates to vancomycin and teicoplanin of respectively 99%-100% and 68%-100% are  
216 found in clinical studies (Del' Alamo et al., 1999; Cuevas et al., 2004; Reynolds et al., 2004;  
217 Chaudhury et al., 2007; Koksai et al., 2007; Sader et al., 2007).

218 Novel antibiotics have been developed to overcome the resistance problem in CNS. These  
219 antibiotics include for example linezolid, daptomycin, tigecycline and quinupristin/dalfopristin.  
220 Susceptibility of CNS isolates towards these agents is usually 100% (Garrison et al., 2005; Sader et  
221 al., 2007). In recent surveillance studies the lowest reported susceptibility percentages are 98,4% for  
222 linezolid (Jones et al., 2007a), 99% for quinupristin/dalfopristin (Jones et al., 2007b) and 99,9% for  
223 daptomycin (Sader et al., 2007). In one institution, 4% of CNS, originating from 25 patients, were  
224 found to be linezolid resistant. The majority of these resistant strains showed some genetic  
225 relatedness, previous linezolid use was an independent predictor of linezolid resistance and the  
226 majority of patients had been accommodated in a single ward (Potoski et al., 2006).

227 The prevalence of resistance varies widely among staphylococcal species. The highest rates  
228 of resistance are found in *S. haemolyticus*: 76-96% oxacillin resistant, 80-90% erythromycin  
229 resistant, 26-29% teicoplanin nonsusceptible (Gill et al., 1983; Del' Alamo et al., 1999; Chaudhury  
230 et al., 2007; Gatermann et al., 2007). Oxacillin resistance rates are also high in *S. hominis* (80%)  
231 (Gatermann et al., 2007) and *S. epidermidis* (38-81%) (Gill et al., 1983; Del' Alamo et al., 1999;  
232 Gatermann et al., 2007). Teicoplanin nonsusceptible isolates occur in 3% of *S. epidermidis* and in  
233 none of the *S. hominis* isolates (Del' Alamo et al., 1999). *S. lugdunensis* has nearly uniform in vitro  
234 susceptibility to most antimicrobials, including penicillins, cephalosporins and macrolides (Poutanen  
235 et al., 2001; Gatermann et al., 2007).

236

## 237 **6. Epidemiology**

238

239 Several studies show that most CNS infections are hospital-acquired or health-care related  
240 (Rupp et al., 1994; Huebner et al., 1999). Colonization of patients and hospital staff with antibiotic  
241 resistant *S. epidermidis* precedes infection with these organisms (Kloos et al., 1994; Nouwen et al.,  
242 1998; Widerström et al., 2006). Some clones are probably endemic in the hospital environment. CNS  
243 have the ability to survive in the intensive care unit (ICU) surroundings on medical devices and  
244 medical equipment for weeks to months (Neely et al., 2000). The clonal spread of identical or closely  
245 related methicillin-resistant CNS strains within hospitals and even between hospitals has been  
246 demonstrated (Monsen et al., 2000; Widerström et al., 2006). Frequent transmission of CNS between  
247 intubated patients was demonstrated in a multidisciplinary ICU (Agvald-Öhman et al., 2004). The  
248 spread of CNS strains is well studied in neonatal ICUs, where CNS are the major causative organism  
249 of sepsis. A relatively small number of molecular types of CNS can persist in the neonatal ICU for  
250 many years. The *mecA* gene carriage in these clusters is usually very high, which suggests that  
251 antibiotic resistance is one of the major selective forces (Krediet et al., 2004). Multi locus sequence  
252 typing identified a sequence type (ST 27), which contained exclusively *ica*-positive isolates and  
253 represented the majority of clinical strains within different hospitals in Germany. The ST 27 clone  
254 was also detected in a Norwegian hospital and in medical facilities in the United States (Kozitskaya  
255 et al., 2005). The combination of biofilm formation, antibiotic resistance and genetic flexibility (due  
256 to multiple copies of IS256) in the ST27 clone may explain why this clone is so predominant in  
257 hospital settings. It is tempting to assume that patients who are admitted to hospital are rapidly  
258 colonized with this clone and that this newly acquired microflora might represent the origin for later  
259 infection (Kozitskaya et al., 2005; Ziebuhr et al., 2006). Hospital personnel can also be responsible  
260 for spreading multi resistant CNS isolates (Hira et al., 2007). Clonal types can only be distinguished  
261 by genotypic methods and not by phenotypic appearance of the colonies or by antibiotype (Nouwen  
262 et al., 1998; Miragaia et al., 2002). Risk factors for the emergence and spread of CNS clones in  
263 hospitals include the duration of hospital stay (especially ICU stay), duration of antibiotic treatment,

264 antibiotic pressure in the environment, and hygienic standards (Widerström et al., 2006). The use of  
265 contact and hand hygiene precautions is extremely important for preventing nosocomial colonization  
266 and infections. Maybe periodic surveillance of patients and staff in specific wards could be useful to  
267 avoid the spread of multi resistant CNS. A good antibiotic policy, in order to reduce the antibiotic  
268 pressure, will help to reduce the incidence of multi resistant CNS.

269

## 270 7. Specific infections

271

### 272 7.1. Urinary tract infections (UTI)

273

274 *S. saprophyticus* is the second (after *Escherichia coli*) most frequent causative organism of  
275 uncomplicated urinary tract infections (UTI) in women. Complications, such as recurrent infection,  
276 acute pyelonephritis, nephrolithiasis, septicaemia and endocarditis have been documented but are  
277 rare (Raz et al., 2005; Widerström et al., 2007). The vast majority of infections occur in young,  
278 sexually active women. *S. saprophyticus* can also cause UTI in males of all ages (Raz et al., 2005). *S.*  
279 *saprophyticus* is found in 3-9% of cases of uncomplicated acute cystitis (Christiaens et al., 1998;  
280 Grude et al., 2005; Nys et al., 2006). Frequency of isolation is age dependent. In a recent study, *S.*  
281 *saprophyticus* was isolated from 7%, 4% and 0.5% of subjects in age categories 11-20 years, 21-50  
282 years and 51-70 years, respectively (Nys et al., 2006). *S. saprophyticus* can be pathogenic in low  
283 numbers ( $<10^5$  cfu/mL) (Rupp et al., 1994). *S. saprophyticus* is probably often missed as causative  
284 organism of UTI, as the bacteriuria is considered to be nonsignificant, especially when bacterial  
285 counts are low.

286 *S. saprophyticus* has also been isolated from 7% of rectal swabs taken from carcasses of  
287 cattle and pigs. The micro-organism is a common contaminant of various food samples, especially of  
288 raw beef and pork (Raz et al., 2005). In humans, the major reservoir of *S. saprophyticus* is the  
289 gastrointestinal tract. The following risk factors have been identified: recent sexual intercourse,

290 outdoor swimming and meat processing (Huebner et al., 1999). Colonization and infection is more  
291 frequent during summer and fall.

292 Other CNS species, mainly *S. epidermidis*, are occasionally found as causative organisms in  
293 UTI (<5% of UTI in hospital environment). *S. epidermidis* is usually isolated from hospitalized,  
294 elderly patients with urinary catheters or other manipulations to the urinary tract (Rupp et al., 1994;  
295 Raz et al., 2005).

296

## 297 7.2. Endocarditis

298

299 The incidence and characteristics of CNS endocarditis were studied in a large cohort of  
300 patients from the International Collaboration on Endocarditis Merged Database (Chu et al., 2004).  
301 CNS accounted for 7% of cases of definite native valve endocarditis (NVE), excluding endocarditis  
302 associated with injection drug use (Chu et al., 2004). Most CNS NVE is caused by *S. epidermidis*  
303 (85%). The remainder is caused by *S. hominis* (6%), *S. lugdunensis* (5%), *S. capitis*, *S. caprae* and *S.*  
304 *simulans*. Rates of heart failure and mortality were found to be similar between patients with CNS  
305 and *S. aureus* NVE (Chu et al., 2004). Patients with NVE caused by staphylococci were significantly  
306 more likely to have health-care associated endocarditis than patients with viridans streptococcal  
307 NVE.

308 In a study from 1999, streptococci are responsible for 48% of cases of infective endocarditis,  
309 *S. aureus* for 23% and CNS for 6% (Hoen et al., 2002). These frequencies were also found in a study  
310 conducted between 1951 and 1965: *S. epidermidis* was the third most frequent isolated organism (in  
311 10% of cases) in cases of bacterial endocarditis, after viridans streptococci (47%) and *S. aureus*  
312 (24%) (Dalton et al., 1967). Injecting heroin users are susceptible to right-sided endocarditis due to *S.*  
313 *epidermidis* (von Eiff et al., 2001).

314 Characteristics of patients with prosthetic valve endocarditis (PVE) were studied and  
315 compared with NVE patients in the International Collaboration on Endocarditis – Prospective Cohort

316 Study (Wang et al., 2007). Patients with PVE had a higher rate of CNS infection (16.9%) than  
317 patients with NVE (8.3%). In literature, higher rates (than in the study by Wang et al., 2007) of CNS  
318 in infections of prosthetic valves are found (40-50% of cases) (Huebner et al., 1999; von Eiff et al.,  
319 2001).

320 *S. lugdunensis* endocarditis has more features of *S. aureus* endocarditis than of CNS  
321 endocarditis. The infection is often aggressive, most cases are community-acquired and only a  
322 minority of patients (approximately 25%) has prosthetic valves (Poutanen et al., 2001).

323

### 324 7.3. Blood stream infections (BSI)

325

326 Almost all cases of bacteremia due to CNS are nosocomial or at least health-care related in  
327 origin. Intravascular and cardiovascular devices, such as peripheral and central catheters, vascular  
328 grafts, implanted defibrillators and coronary stents, are widely used. Catheter related infections are  
329 by far the most common cause of bacteremia due to CNS (Huebner et al., 1999).

330 Throughout the 1960s and 1970s, Gram-negative organisms were the most common pathogens  
331 isolated from patients with nosocomial blood stream infections (BSI) (Wisplinghoff et al., 2004), but  
332 in one study (Dalton et al., 1967), between 1951 and 1965, *S. epidermidis* accounted for 23% of  
333 positive blood cultures in patients with suspected bacteremia. Second and third most frequent  
334 isolated organism was *S. aureus* (12%) and *Corynebacterium* species (12%). The high rates of  
335 common skin bacteria (such as *Corynebacterium* species and *S. epidermidis*) in the study by Dalton  
336 et al., 1967, raise concern about the clinical significance. The incidence of bacteremia caused by  
337 CNS rose between 161% and 754%, respectively in large teaching and small non-teaching hospitals,  
338 between 1980 and 1989 (Rupp et al., 1994). During 1986 - 1989 CNS were the most frequently  
339 reported cause of BSI, accounting for 27% of BSI (Schaberg et al., 1991).

340 In a nation wide surveillance study in the USA, performed between 1995 and 2002, CNS  
341 accounted for 31% of all nosocomial BSI (Wisplinghoff et al., 2004). The crude mortality of BSI due

342 to CNS was 25.7% in an intensive care unit (ICU) and 13.8% in a non-ICU ward. In Flanders,  
343 Belgium, CNS account for 25.9% of all nosocomial BSI. Forty-eight percent of BSI cases in  
344 Flanders were due to catheter related sepsis, 32% to sepsis of unknown origin, and 20% were  
345 associated with another infection or an invasive manipulation (Suetens et al., 2002).

346 CNS are the most common pathogens in catheter-related infections (50-70% of cases). In  
347 addition to bacteremia, CNS, mainly *S. epidermidis*, can cause exit-site infections, tunnel infections,  
348 infected thrombophlebitis, endocarditis and abscesses (Rupp et al., 1994; Huebner et al., 1999). At  
349 the time of removal, 8-40% of all catheters are colonized by CNS (Rupp et al., 1994).

350 Positive blood cultures with CNS can be explained by contamination, true bacteremia or transient  
351 benign bacteremia (Rupp et al., 1994). It may be very difficult to distinguish between infection and  
352 contamination. As the positive predictive value of a blood culture growing CNS varies from 6 to  
353 12% (Correa et al., 1999), the criteria used for defining true bacteremia influence reported CNS  
354 prevalence. The CDC criteria for defining bloodstream infection (Garner et al., 1988) are used in  
355 most of the studies. The intensity of surveillance also influences the reported BSI incidence and  
356 prevalence of CNS.

357 There is increasing evidence that the mucosa, rather than skin, is the likely source of CNS  
358 bacteremia in cancer patients (Costa et al., 2004; Costa et al., 2006). A recent study showed that  
359 among cancer patients with CNS positive blood cultures and an indwelling central venous catheter  
360 (CVC), the mucosal sites were the most frequently colonised by CNS (nasal mucosa in 86%, rectal  
361 mucosa in 40%). The skin at the CVC site was colonised by CNS in 32% of patients. Among patients  
362 with true bacteremia, 6 mucosal isolates and only 1 skin isolate were genetically related to the isolate  
363 recovered from blood based on pulsed-field gel electrophoresis (Costa et al., 2006). A review of the  
364 literature confirms that CNS colonise mucosal sites including gut, nares and throat and may  
365 translocate from mucosal sites to the bloodstream (Costa et al., 2004). This is supported by  
366 epidemiological, experimental, clinical and molecular relatedness studies. The assumption that the  
367 skin is the primary source of CNS infection has been the reason to try to achieve a reduction of CNS

368 catheter related bacteremia with skin decontamination and the use of maximum barrier precautions at  
369 the time of CVC insertion. However, not all studies show a positive effect of these two interventions  
370 (Costa et al., 2004).

371

#### 372 7.4. Foreign body-related infections (FBRIs)

373

374 Insertion or implantation of medical devices is associated with a risk of bacterial and fungal  
375 infections. Medical devices are increasingly used in almost all fields of medicine for diagnostic  
376 and/or therapeutic procedures. The contamination of the device occurs most likely by inoculation  
377 with only a few micro-organisms from the patient's skin or mucous membranes during implantation  
378 or subsequent manipulations (Rupp et al., 1994; von Eiff et al., 2001; von Eiff et al., 2005). The  
379 pathogens may also be acquired from the hands of the surgical or clinical staff (von Eiff et al., 2005).  
380 Staphylococci, particularly *S. epidermidis*, account for the majority of FBRIs (von Eiff et al., 2005).  
381 Most CNS isolates causing foreign body-related infections (FBRI) are methicillin resistant.

382 Neurosurgical devices (ventricular shunts, implantable stimulators, intracranial pressure  
383 devices) are frequently used. Of the pathogens isolated from ventriculoperitoneal shunt infections in  
384 pediatric patients less than 8 years old, 53% were CNS (Filka et al., 1999). Clinical symptoms can be  
385 subtle and nonspecific. (Huebner et al., 1999). In a review of CSF shunt infections, caused by a  
386 single pathogen, CNS and *S. aureus* were isolated with equal frequency, i. e. in 23% of cases each  
387 (Wang et al., 2004). Others reported that CNS are the most common cause of shunt infections (40-  
388 60% of infections) (Rupp et al., 1994). In a retrospective study, pure culture of CNS accounted for  
389 11% of cases of adult bacterial meningitis (Huang et al., 2005). All cases had post-neurosurgical  
390 states as underlying condition.

391 CNS cause 17-56% of episodes of continuous ambulatory peritoneal dialysis-associated  
392 peritonitis (Rupp et al., 1994, Monsen et al., 2000). *S. epidermidis* is the predominant species (78%)  
393 followed by *S. haemolyticus* (11%) (Monsen et al., 2000). From 1991 to 1998, the incidence of

394 dialysis-related peritonitis caused by *S. epidermidis* decreased, probably due to the introduction of a  
395 new dialysis system. Even so, *S. epidermidis* was still the most common cause of peritonitis in 1998,  
396 causing 28% of culture positive cases (Zelenitsky et al., 2000).

397 Up to 60% of vascular graft infections and 20-40% of prosthetic joint infections are caused  
398 by CNS (Rupp et al., 1994).

399 CNS are also associated with low grade foreign body infections such as aseptic loosening of hip or  
400 other joint prostheses, or fibrous capsular contracture syndrome after mammary augmentation with  
401 silicone prostheses (von Eiff et al., 2001).

402

#### 403 7.5. Surgical site infection

404

405 *S. aureus* is the most common pathogen isolated from surgical site infections (SSI) (20%),  
406 followed by CNS (14%) and *Enterococcus* species (12%) (CDC, 1996). In a secondary care hospital,  
407 CNS were the third (10%) most frequently isolated micro-organism, after *S. aureus* (21%) and  
408 *Streptococcus* species (11.2%) (Cantlon et al., 2006). Outbreaks of SSI originating from operating  
409 room personnel have been reported, but probably most infections are indogenous (Huebner et al.,  
410 1999). Sternal osteomyelitis following median sternotomy is caused predominantly by CNS (Rupp et  
411 al., 1994).

412

#### 413 7.6. Endophthalmitis

414

415 CNS are by far the most common pathogens isolated from vitreous biopsies in cases of  
416 endophthalmitis. In a review of 67 cases of endophthalmitis, 31% of the culture positive biopsies  
417 (only 44%) yielded CNS as pathogen (Karacal et al., 2007). Most cases of endophthalmitis were  
418 postoperative (73.5%), mainly after cataract surgery. Other cases were associated with endogenous  
419 origin (13%), post-intravitreal injection (6%), keratitis (4%) and post-traumatic (3%). Post-traumatic

420 endophthalmitis, a complication of a penetrating eye injury, is caused by CNS in 28% of cases (Abu  
421 El-Asrar et al., 1999).

422

### 423 7.7. Mastitis

424

425 CNS are rarely associated with mastitis in humans. In lactation mastitis, the agents most  
426 frequently cultured from milk are *S. aureus* and CNS (Barbosa-Cesnik et al., 2003). In non  
427 lactational breast abscesses, CNS are rarely isolated as sole pathogen. Some cases of non lactational  
428 breast abscesses, especially with *S. lugdunensis* have been published in literature (Asnis et al., 2003).  
429 *S. aureus* and anaerobes are the most common organisms to cause breast abscesses (Surani et al.,  
430 1993).

431

## 432 8. Conclusions and Outlook

433

434 CNS are a group of micro-organisms that are increasingly implicated as a cause of significant  
435 infection. The infection rate has been correlated with the increase in the use of invasive and  
436 indwelling medical devices and the growing number of immunocompromised patients. Community  
437 acquired, primary CNS infections are rare, except for *S. saprophyticus* UTI, NVE and *S. lugdunensis*  
438 infections. The increase of CNS infections is particularly high in bacteraemia. CNS are now a major  
439 cause of nosocomial or health care related infections. The consequences of these infections are  
440 substantial, both in morbidity and mortality and in financial costs. Clonal spread of CNS clusters  
441 within and even between hospitals has been demonstrated. This is of major concern as CNS are often  
442 multi-drug resistant and can serve as a reservoir of resistance genes. Implementation of infection  
443 control measures similar to those used for MRSA may be necessary to prevent further spread of  
444 methicillin and multi-drug resistant CNS.

445

446

447 **Conflict of Interest**

448

449 None of the authors (A. Piette, G. Verschraegen) has a financial or personal relationship with  
450 other people or organizations that could inappropriately influence or bias the paper entitled “Role of  
451 coagulase-negative staphylococci in human disease”.

452

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689 Table 1

690 Species distribution (%), sample origin, used identification method of CNS in clinical samples in different studies (country and publication date in  
691 heading).

	USA 1983 (1)	USA 1993 (2)	Denmark 1996 (3)	Japan 1998 (4)	Brazil 1999 (5)	Spain 2004 (6)	France 2005 (7)	India 2006 (8)	India 2007 (9)	Germany 2007 (10)	Turkey 2007 (11)
<i>S. epidermidis</i>	75	65	58	50	50	56	71	34	13	67	44
<i>S. haemolyticus</i>	7	13	9	16	10	5	2	13	72	12	12
<i>S. hominis</i>	5	7	12	5	12	18	4	2	6	9	9
<i>S. simulans</i>	1	2		6		1	1		2	1	2
<i>S. capitis</i>	2	4	<1	5		3	6	10	1	1	8
<i>S. saprophyticus</i>	1	1	1	5		5				<1	3
<i>S. warneri</i>	3	4	2	3		4	7	1	1	2	4
<i>S. lugdunensis</i>		3	<1	2			3	13	1	3	9
<i>S. caprae</i>				14			2			1	
<i>S. cohnii</i>	<1	1	1	<1	6	0	<1			1	<1
<i>S. auricularis</i>		<1		<1							<1
<i>S. schleiferi</i>								12		1	<1
<i>S. xylois</i>						0		6		1	5
<i>S. pasteurii</i>							2				
sample origin	CS	CS	BSI	CS	BSI		BJI	CS	CS	BSI	BSI
identification method	SP	Vitek1	SP	DNA	Microsc	SP	<i>sodA</i>	SP	Vitek2	SP + <i>sodA</i>	API

692 (1) Gill et al. (2) Kleeman et al. (3) Jarløv et al. (4) Kawamura et al. (5) Del' Alamo et al. (6) Cuevas et al. (7) Sivadon et al. (8) Singhal et al. (9)  
693 Chaudhury et al. (10) Gatermann et al. (11) Koksai et al.; CS: clinical specimens, BJI: bone and joint infections; SP: standard procedures (based on  
694 Kloos and Schleifer), Vitek1: Vitek GP card (Biomérieux), *sodA*: *sodA* sequencing, DNA: DNA-DNA hybridization, Microsc: Microscan positive  
695 combo panel type 6 (DADE MicroScan Inc., Sacramento, CA), Vitek2: Vitek ID 32 Staph (Biomérieux), API: API ID 32 Staph (Biomérieux)

696

696 Table 2

697 Percentage susceptibility of CNS in different studies (in heading country and publication date); MR: % susceptibility in methicillin resistant strains, MS:

698 % susceptibility in methicillin susceptible strains

% susceptibility	Spain	UK, Ireland		Asia_Pacific		USA	Europe, Asia,	Turkey		Europe, Turkey,	
	2002 (1)	2004 (2)		region 2007 (3)		2007 (4)	Australia, Latin	2007 (6)		Israel 2007 (7)	
		MR	MS	MR	MS		America 2007 (5)	MR	MS	MR	MS
methicillin/oxacillin	39	24		15,2		23,1	25,7	32,5		28	
penicillin	21	0	24.5			12.1	15.3	0	9		
ceftriaxone						51.1	47.6				
ciprofloxacin	55	40.8	81.6			42.2	46.5	33	77	27.8	86.9
levofloxacin				50.2	89.1	42.3	47.5			28.1	87.3
cotrimoxazole	76			60.8	89.1	61.9	59.3	32	62	52.6	91.8
gentamicin	72	25.7	78.6			71.3	57.7	10	83		
tetracycline		39.2	67.3	83.5	89.1	86.9	83.7	40	55		
erythromycin	37	27.3	62.2	31.8	78.3	28.8	33.8	20	63	27.2	65.7
clindamycin	66	69.1	93.9	68.6	95.7	59.9	60.7	28	82	67	94.8
chloramphenicol	91			87.1	91.3			44	87	86.6	97.4
fusidic acid								75	85		
rifampicin	93									85.3	96.1
teicoplanin	100	65	77.6	96.1	89.1	99.3	99.3	100	100	97.3	99.6
vancomycin	100	99.7	100	100	100	100	100	100	100	100	100
linezolid	100	100	100	100	100	98.4	99.5			100	100
quinupristin/dalfopristin	100			99.6	100	99.3	99			99.3	100
daptomycin						100				100	99.6

699 (1) Cuevas et al. (2) Reynolds et al. (3) Biedenbach et al. (4) Jones et al., 2007a (5) Jones et al., 2007b (6) Koksall et al. (7) Sader et al.